Modifiable risk factors for intracerebral hemorrhage

Study of anticoagulated patients

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ABSTRACT

OBJECTIVE To determine whether there are modifiable risk factors for spontaneous intracerebral hemorrhage in patients receiving oral anticoagulation (OAC) therapy.

DESIGN Retrospective chart review between January 2002 and December 2004.

PARTICIPANTS A total of 315 consecutive patients presenting with spontaneous intracerebral hemorrhage.

MAIN OUTCOME MEASURES Overall mortality rates and surgical mortality rates, and discharge home compared with discharge to a long-term care facility.

RESULTS Of the 315 patients reviewed, 65 (20.6%) were receiving OAC therapy. Age, Glasgow Coma Scale score, and size of hematoma at presentation were similar in the 65 patients taking OAC and the 250 patients not taking it. Mean arterial pressure at presentation was significantly higher in the OAC group than in the control group (132 mm Hg vs 107 mm Hg, $P=.01$) as was the number of hematomas that progressed (52% vs 14%, $P=.01$). Overall mortality rates were higher in the OAC group than in the control group (52% vs 41%, $P=.03$) as were surgical mortality rates (62% vs 41%, $P=.04$). There were no significant differences in morbidity between the 2 groups.

CONCLUSION Mortality rates were higher among patients taking OAC therapy despite their having similarly sized hematomas at presentation. The higher initial mean arterial pressure among such patients has not been described previously in this setting. This higher mean arterial pressure correlates with the propensity of these patients' hematomas to expand after initial imaging and might partially mediate the mortality effect. In patients taking OAC, hypertension appears to be a modifiable risk factor for morbidity and mortality from intracerebral hemorrhage.

EDITOR'S KEY POINTS

- This study looked at whether there are modifiable risk factors that could be addressed to protect patients taking oral anticoagulation (OAC) medication from the morbidity and mortality of intracerebral hemorrhage.
- Hematoma size on initial presentation was similar in both patient groups. The proportion of hematomas that progressed was significantly larger among patients taking OAC (52%) than among patients in the control group (14%).
- Predictors of mortality were age at presentation, use of OAC, mean arterial pressure at presentation, and posterior fossa location of the hematoma.

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Facteurs de risque modifiables pour l'hémorragie cérébrale

Étude de patients anticoagulés

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RÉSUMÉ

OBJECTIF Établir s'il existe des facteurs de risque modifiables pour l'hémorragie cérébrale spontanée chez des patients traités par anticoagulants oraux (ACO).

TYPE D'ÉTUDE Étude rétrospective sur dossier entre janvier 2002 et décembre 2004.

PARTICIPANTS Un total de 315 patients consécutifs avec un diagnostic initial d'hémorragie cérébrale spontanée.

PRINCIPAUX PARAMÈTRES ÉTUDIÉS Taux global de mortalité et taux de mortalité chirurgicale, et retour à la maison au congé vs hébergement en établissement de soins prolongés.

RÉSULTATS Sur les 315 patients étudiés, 65 (20,6%) recevaient des ACO. L'âge, le score à l'échelle de Glasgow et la taille de l'hématome étaient semblables à l'arrivée pour les 65 patients recevant des ACO et les 250 n'en recevant pas. La tension artérielle moyenne initiale était significativement plus élevée dans le groupe ACO que dans le groupe témoin (132 vs 107 mm Hg, *P*=0,01) de même que le nombre d'hématomes ayant progressé (52% vs 14%, *P*=0,01). Dans le groupe ACO, le taux global de mortalité était plus élevé que dans le groupe témoin (52% vs 41%, *P*=0,03); le taux de mortalité chirurgicale était aussi plus élevé (62% vs 41%, *P*=0,04) dans ce groupe. Il n'y avait pas de différence significative de morbidité entre les deux groupes.

CONCLUSION Les patients prenant des ACO avaient un plus fort taux de mortalité, même si la taille initiale des hématomes était la même. La plus forte tension artérielle moyenne initiale chez ces patients semble être une observation nouvelle dans un tel contexte. Cette valeur de tension artérielle moyenne plus élevée est corrélée au fait que chez ces patients, les hématomes ont tendance à progresser après l'examen d'imagerie initial, ce qui pourrait contribuer à l'effet sur la mortalité. L'hypertension chez un patent traité aux ACO semble constituer un facteur de risque modifiable de morbidité et de mortalité par hémorragie cérébrale.

POINTS DE REPÈRE DU RÉDACTEUR

- Cette étude voulait établir s'il existe des facteurs de risque modifiables auxquels on pourrait s'attaquer pour réduire les problèmes de morbidité et de mortalité par hémorragie cérébrale chez les patients traités par anticoagulants oraux (ACO).
- La taille initiale des hématomes était la même dans les deux groupes de patients. Chez ceux recevant des anticoagulants oraux, la proportion des hématomes ayant progressé était significativement plus élevée que chez ceux du groupe témoin (52% vs 14%).
- Les facteurs prédictifs de mortalité étaient l'âge et la tension artérielle moyenne aux premières manifestations, la prise d'ACO et la localisation de l'hématome dans la fosse postérieure.

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Intracerebral hemorrhage (ICH) is a life-threatening condition that is associated with substantial morbidity and mortality. The initial hematoma, associated brain edema, and subsequent expansion of the hematoma can lead to neurologic dysfunction and increased intracranial pressure. This disease can affect the brain parenchyma or can be present within the surrounding meningeal space. Intracranial hemorrhage, or hemorrhagic stroke, accounts for 10% to 15% of all cerebrovascular accidents.[1] It is classified as primary or secondary. Primary ICH is spontaneous; secondary ICH occurs because of underlying disease, such as vascular malformation or neoplasm. The incidence of ICH is 15 to 19 cases per 100 000 people in the general population[2] and up to 200 cases per 100 000 people among the elderly.[3] The associated 30-day mortality rate ranges between 40% and 50%.[2]

The most common cause of primary ICH is damage to blood vessel walls as a result of hypertension.[4] Chronic hypertension leads to small-vessel vasculopathy with lipohyalinosis of the blood vessels, fibrinoid necrosis, and the development of small arterial dilations known as miliary aneurysms.[4,5] Rupture of these damaged vessels is thought to be the ictal event leading to ICH.[5] It is not surprising that mortality from ICH correlates positively with mean arterial pressure at presentation. Mortality rates are 21% with a mean arterial pressure < 145 mm Hg and 47% with a mean arterial pressure ≥ 145 mm Hg.[6] Hematoma enlargement was noted in 40% of patients with high systolic blood pressure (> 160 mm Hg)[7] but in only 20% of patients in the general population.[8]

Another causal factor of particular importance to family physicians is that use of OAC therapy increases the risk of ICH 7- to 10-fold.[9] Warfarin is the most frequently prescribed oral anticoagulant and also the fourth most commonly prescribed cardiovascular drug.[10] It is indicated mostly for patients with cardiac arrhythmias, venous thrombosis, mechanical heart valves, and pulmonary embolism. One of the characteristics of warfarin is its complex dose-response relationship that necessitates frequent monitoring by measuring patients' international normalized ratios (INRs). Use of warfarin is further complicated by the narrow therapeutic range for its indications. A supratherapeutic INR can result from drug-drug interactions, such as with chemotherapeutic agents,[11] antibiotics, antifungals, ethanol, and salicylates.[10] Studies have established that use of OAC therapy is an independent risk factor for intracerebral hematoma expansion and death.[12,13] The mortality rate after ICH in anticoagulated patients is 60%,[8] exceeding the 40% observed in patients not taking OAC.[14] This study explores whether there are modifiable risk factors that could be addressed to protect patients taking OAC medications from the morbidity and mortality of ICH.

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METHODS

This was a retrospective study of the charts of 315 consecutive patients with nontraumatic ICH who presented to the Ottawa Hospital in Ontario between January 2002 and December 2004. Ethics approval was obtained from the Ottawa Hospital Research Ethics Board. The Ottawa Hospital is a level 1 trauma centre that admits patients both directly through its emergency department and from other smaller regional hospitals. Our inclusion criteria were that patients had to be older than 18 years and that the ICH had to be of nontraumatic origin. Exclusion criteria included subdural hematoma and other serious intracranial trauma.

Patients were stratified into control (n = 250) and anticoagulated (n = 65) groups. Several clinical variables were collected, including demographic information, Glasgow Coma Scale score,[15] mean arterial pressure at first presentation, anticoagulation use and indication, as well as INR at first presentation. Computed tomography (CT) variables included results of initial CT scans and repeat CT scans at 24 hours to assess progression of bleeding and size[16] and location of hematomas. The OAC and control groups were then further stratified into patients with a mean arterial pressure < 145 mm Hg and those with a mean arterial pressure ≥ 145 mm Hg. Management variables included medical management with or without surgical intervention. Outcomes assessed were death, discharge to an assisted-living facility, or discharge home.

Student *t* tests were used to evaluate differences in demographic variables between control and OAC groups, and χ^2 tests were used for Glasgow Coma Scale scores and INRs. Student *t* tests were used to assess differences in hematoma size and likelihood of growth. Hematoma location was assessed using nominal logistic regression between control and OAC groups. Outcomes were compared using Student *t* test for likelihood of surgical intervention and single-factor analysis of variance for discharge and mortality outcomes. Multivariate regression analysis was used to assess overall and surgical mortality rates.

RESULTS

Of the 315 consecutive patients reviewed, 65 (21%) were being managed with OAC (**Table 1**). The INRs of 57 (88%) of the patients taking OAC were in the infratherapeutic or therapeutic range; the other 8 (12%) patients' INRs were in the supratherapeutic range. The most common indications for warfarin use were atrial fibrillation (37 patients, 57% of the OAC group), mechanical heart valve (19 patients, 29% of the OAC group), and transient ischemic attack (2 patients, 3% of the OAC group). The indication for warfarin could not be determined for 7 patients taking OAC (11%) .

Age and Glasgow Coma Scale scores were similar in both OAC and control groups (**Table 1**). Mean arterial pressure at first presentation was significantly higher ($P=.01$) among patients in the OAC group (132 mm Hg, 95% confidence interval [CI] 91 to 173 mm Hg) than among controls (107 mm Hg, 95% CI 76 to 138 mm Hg). As expected, INRs were also higher in the OAC group (2.6, 95% CI 1.2 to 4.0) than in the control group (1.0, 95% CI 0.8 to 1.2) ($P=.01$).

The size of hematomas on initial presentation was similar in both groups (**Table 2**). The proportion of hematomas progressing, measured by hematoma expansion of 40%, was significantly larger in the OAC group (52%) than in the control group (14%) ($P=.01$). The locations of hematomas are listed in **Table 3.** There were more spontaneous intracerebral bleeds in the cerebellum in the OAC group than there were in the control group (odds ratio 3.17, 95% CI 1.24 to 8.90), which is consistent with findings in the literature.[17]

In both control and OAC groups, the number of patients whose disease progressed was significantly higher among those with a mean arterial pressure ≥145 mm Hg than among those with a mean arterial pressure <145 mm Hg (**Table 2**). Among OAC patients, disease progressed in 72% of hypertensive patients and in only 40% of normotensive patients ($P<.01$). Similarly in the control group, disease progressed in 34% of hypertensive patients and in only 10% of normotensive patients ($P=.001$).

Management of ICH included both medical and surgical therapy. Surgical management involved craniotomy with evacuation of the clot. Medical management included normalization of coagulation status and blood pressure control. In this study, 25% of OAC patients required surgical intervention compared with only 14% of control patients (**Table 4**). Higher surgical and overall mortality rates were observed among anticoagulated patients (62% and 52%, respectively) than among control patients (41% and 41%, respectively) ($P<.01$), although no differences in overall and surgical morbidity were

Table 1. Patient characteristics

VARIABLES AT PRESENTATION	PATIENTS TAKING OAC (N = 65)	CONTROL PATIENTS (N = 250)	*P* VALUE
Mean age, y (95% CI)	71 (44-98)	64 (35-93)	.09
Mean arterial pressure, mm Hg (95% CI)	132 (91-173)	107 (76-138)	.01*
Median Glasgow Coma Scale score (interquartile range)	14 (13-15)	13 (8-15)	.15
Mean INR (95% CI)	2.6 (1.2-4.0)†	1.0 (0.8-1.2)	.01

CI—confidence interval, INR—international normalized ratio, OAC—oral anticoagulation.
*Statistically significant by Student *t* test, $P<.05$.
†Of the patients taking OAC, 19 had INRs <2, 38 had INRs between 2 and 3, and 8 had INRs >3.

Table 2. Imaging results for patients with high and low MAP in the OAC and control groups

IMAGING RESULTS	PATIENTS TAKING OAC* N = 65			CONTROL PATIENTS* N = 250		
	MAP <145 MM HG	MAP ≥145 MM HG	ALL PATIENTS TAKING OAC	MAP <145 MM HG	MAP ≥145 MM HG	ALL CONTROL PATIENTS
Mean size of hematoma on initial CT scan, cm^3 (95% CI)	34 (3-65)	50 (9-91)†	42 (7-77)	35 (8-62)	47 (16-78)‡	38 (9-67)
No. of hematomas progressing (%)	16/40 (40)	18/25 (72)†	34/65 (52)	18/177 (10)	13/38 (34)§	31/215 (14)‖

CI—confidence interval, CT—computed tomography, MAP—mean arterial pressure, OAC—oral anticoagulation.
*$P=.24$ for the difference in initial mean size of hematomas and $P=.01$ for the difference in the number of hematomas progressing between the OAC and control groups.
†$P=.001$ for the difference in initial mean size of hematomas and number of hematomas progressing between high and low MAP in the OAC group.
‡$P=.002$ for the difference in initial mean size of hematomas between high and low MAP in the control group.
§$P=.001$ for the difference in the number of hematomas progressing between high and low MAP in the control group.
‖35 patients in the control group did not have follow-up CT scans from which to gauge progression of hematomas.

observed between groups in terms of discharge home versus discharge to a long-term care facility.

In multivariate regression analysis, age at presentation (F=4.4, P=.037), use of OAC (F=3.9, P=.049), mean arterial pressure at presentation (F=14.1, P<.01), and posterior fossa location of hematoma (F=4.25, P=.04) were independent predictors of mortality.

DISCUSSION

Most patients with ICH treated with warfarin had INR values that were either infratherapeutic or therapeutic (57 of 65 patients). Oral anticoagulation as a risk factor for ICH, regardless of INR value, has been described in the literature as an "all or nothing effect with a low threshold."[18] Morbidity, as measured by need for long-term assisted care, and mortality rates of ICH were much higher in the OAC group than they were in the control group. Those in the OAC group more often required surgical intervention and had higher overall and surgical mortality rates. The decision to proceed with surgical intervention was largely based on clinical deterioration resulting from disease progression, which was observed in 52% of patients taking OAC but in only 14% of control patients.

Although the initial size of the hemorrhages was similar, the location of bleeds was different in the 2 groups. Patients in the OAC group had a greater proportion of bleeds in the cerebellum. Such predilection for the posterior fossa location of hematomas in anticoagulated patients has been reported previously by Flaherty et al,[19] who also described these patients as having heightened immediate and long-term (longer than 1 year) mortality. Hematoma location was associated with the heightened mortality observed for posterior fossa location as expected, but multivariate analysis showed that mean arterial pressure at presentation further predicted increased mortality. While the volume of hematomas was not found in this analysis to be independently associated with mortality, our study was not sufficiently powered to detect an independent effect of this factor.

There was a higher incidence of hypertension among patients taking OAC. The most common indication for OAC in this study was atrial fibrillation, which suggests that some of these anticoagulated patients suffered from underlying cardiovascular disease. This could partly explain the greater association between ICH and hypertension in the OAC group as compared with the control group. The elevated mean arterial pressure at presentation could also represent reflexive hypertension after the bleed to maintain cerebral perfusion, but this is unlikely. Measures of mean arterial pressure in both OAC and control groups were taken at initial presentation when imaging showed hematomas of equal size in both groups. A mean arterial pressure ≥145 mm Hg was implicated in the expansion of hematomas and was an independent predictor of mortality among patients taking OAC. Disease progression was most prevalent among OAC patients who were also hypertensive (mean arterial pressure ≥145 mm Hg); most of these patients' hematomas expanded, and the patients suffered the attendant morbidity and mortality.

Several key studies have examined the relationship between blood pressure and ICH. The Keio Cooperative Stroke Study[20] examined the prognostic value of blood pressure on admission in patients with acute ICH with particular attention to the location of hemorrhages. The researchers concluded that increased blood pressure in putaminal and thalamic bleeds was associated with increased mortality. A study conducted by Fogelholm et al[7] evaluated several prognostic indicators in patients

Table 3. Location of hematomas: *Patients taking oral anticoagulants had an odds ratio of 3.17 (95% confidence interval 1.24-8.90,* P *=.046) for having hematoma bleeds into the cerebellum.*

LOCATION OF HEMATOMA	PATIENTS TAKING ORAL ANTICOAGULANTS (N=65) N (%)	CONTROL PATIENTS (N=250) N (%)
Cerebellum	19 (29.2)	36 (14.4)
Lobar region	15 (23.1)	97 (38.8)
Basal ganglia	18 (27.7)	62 (24.8)
Thalamic area	7 (10.8)	42 (16.8)
Brainstem	6 (9.2)	13 (5.2)

Table 4. Management and discharge outcomes

DISCHARGE	PATIENTS TAKING OAC (N=65) N (%)	CONTROL PATIENTS (N=250) N (%)	*P* VALUE FOR OAC VS CONTROL PATIENTS	PATIENTS TAKING OAC NEEDING SURGERY (N=16) N (%)	CONTROL PATIENTS NEEDING SURGERY (N=34)* N (%)	*P* VALUE FOR OAC PATIENTS NEEDING SURGERY VS CONTROL PATIENTS NEEDING SURGERY
Discharged home	8 (12.3)	54 (21.6)	.22	3 (18.8)	5 (14.7)	.12
Discharged to long-term care facility	23 (35.4)	93 (37.2)	.22	3 (18.8)	15 (44.1)	.12
Died in hospital	34 (52.3)	103 (41.2)	.03	10 (62.5)	14 (41.2)	.04

OAC—oral anticoagulation.
*P=.04 for the difference between the number of patients taking OAC needing surgery and the number of control patients needing surgery.

with spontaneous supratentorial ICH. That study showed that first-day mean arterial pressure was the most important predictor of 28-day survival. A systematic review conducted by Willmot et al[21] also showed that death from ICH was strongly associated with elevated mean arterial pressure. Our investigation examined the mean arterial pressure upon admission of anticoagulated patients and compared it with the mean arterial pressure of non-anticoagulated patients to verify whether mean arterial pressure at presentation was an independent risk factor for the morbidity and mortality of ICH above and beyond the risk of anticoagulation alone. Our results indicated that mean arterial pressure was indeed an independent and modifiable risk factor for mortality and morbidity in anticoagulated patients with ICH. This had not been described previously in the literature.

The recent introduction of activated factor VII, which allows for rapid reversal of INR after the initial presentation of ICH, is an important therapeutic advance. It could moderate many of the ill effects of ICH in anticoagulated patients. Our initial intention was to investigate whether there were modifiable risk factors for morbidity and mortality of ICH in these patients. We found that hypertension remained a clearly modifiable risk factor and should be treated aggressively in this context.

Limitations

One of the limitations of this study was that it was retrospective and, therefore, included variable treatment practices (medical versus surgical) and evolving management strategies. In addition, the study was conducted at a tertiary care centre, which might mean our results would not be generalizable to peripheral centres. Last, we were unable to compare surgical and overall discharge outcomes (discharge home versus discharge to assisted living facilities) in control and OAC groups owing to small numbers, and so no conclusions can be derived from these data.

Conclusion

Overall mortality rates and surgical mortality rates were higher among patients with ICH treated with OAC. The strong relationship between hypertension and the expansion of hematomas was confirmed in this study. In primary care settings, OAC is indicated for primary management of a variety of common diseases. Given that use of OAC is an independent risk factor for morbidity and mortality in patients with ICH, primary care physicians can protect their patients from catastrophic outcomes by ensuring rigorous management of risk factors. This study confirmed that hypertension was an independent risk factor for morbidity and mortality in anticoagulated patients who had consistently higher baseline blood pressure readings at time of presentation. Mortality was most often associated with mean arterial pressure ≥145 mm Hg. This comorbidity should be managed aggressively in those taking OAC therapy as part of a primary prevention strategy related to ICH.

Contributors

Dr Fric-Shamji *contributed to designing the study, reviewing the charts, collecting and interpreting the data, and writing the manuscript.* **Dr Shamji** *contributed to interpreting the data, analyzing the statistics, and reviewing the manuscript.* **Dr Benoit** *contributed to designing the study and reviewing the manuscript, and acted as Supervising Attending Surgeon.* **Mr Cole** *designed software to aid data collection and organization and reviewed the manuscript.*

Competing interests

None declared

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